UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/579,548 | 05/26/2000 | Alan H. Lazarus | 701826/50750 | 7491 |

7590 08/11/2003

David S Resnick
Nixon Peabody LLP
101 Federal Street
Boston, MA 02110

| EXAMINER | |
|---|---|
| GAMBEL, PHILLIP | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | 20 |

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/579548 | Applicant(s) LEMOS |
|---|---|---|
| | Examiner GIMIE | Art Unit 1644 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 5/21/03

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☑ Claim(s) _____ is/are pending in the application. 24, 26, 27, 29, 30

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 24, 26, 27, 29, 30

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☑ All b)☐ Some * c)☐ None of:

1.☑ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:





PAPER NO. 20

## DETAILED ACTION

1. Applicant's amendment, filed 5/21/03 (Paper No. 19), has been entered.
Claims 25, 28 and 31-33 have been canceled. Claims 1-23 have been canceled previously.
Claims 24, 27 and 29 have been amended.

Claims 24, 26, 27, 29 and 30 are pending.

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 24, 26, 27, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Given applicant's amended claims limiting the claimed methods to the administration of soluble 18KDa recombinant human CD40L consisting of amino acids 108-261 set forth in SEQ ID NO: 1, which has been recognized as a CD40 agonist, the instant methods are subject to the enablement rejection set forth herein. As applicant notes, the 18KDa CD40L was known in the part prior to the filing of this application to be a homotrimer (oligomer)in solution, as set forth in Mazzei et al. (J. Biol. Chem. 270: 7025-7028,1995)

Therefore, applicant has amended the claims to limit the soluble CD40L to a known oligomeric CD40L agonists and away from the referenced soluble monomeric CD40L antagonists.

It is acknowledged that the present invention shows that the 18KDa CD40L inhibits a secondary alloimmune response in an SCID experimental model engrafted with human lymphocytes which indicates that oligomeric 18 KDa CD40L is an antagonist rather than a CD40 agonist in a platelet HLA alloimmune immunization model.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as costimulatory-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of inhibiting a secondary alloimmune response in an SCID experimental model engrafted with human lymphocytes would be predictive of treating the breadth of alloimmune responses, T cell responses, autoimmune diseases encompassed by the claimed methods.

There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed therapeutic strategies to inhibit alloimmune responses, T cell responses, autoimmune diseases, commensurate in scope with the therapeutic methods encompassed by the claimed methods.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

As applicant acknowledges, the administration of soluble 18KDa recombinant human CD40L consisting of amino acids 108-261 set forth in SEQ ID NO: 1 has been recognized as a CD40 agonist.

For example, Aruffo et al. (U.S. Patent No. 6,376,459) discloses that treating subject associated with B cell activation comprise administering a ligand such as an antibody that binds CD40CR / CD40L and that CD40CR / CD40L was useful to promote B cell activation (see columns 15-18; Uses of Ligands That Bind to CD40CR and Uses of CD40CR). Here, the therapeutic endpoints and diseases targeted by employing CD40L antagonists and agonists are in direct contrast with the claimed use of soluble 18 KDa CD40L to inhibit cell mediated immune responses, including the use of soluble 18 KDa CD40L in treating or preventing diseases selected from the group set forth instant claim 30.

In addition, Aruffo et al. (U.S. Patent No. 5,540,926) (prior art of record) discloses that soluble gp39 may be used to increase an immune response as a type of adjuvant, while immunosuppression by my accomplished by modifying or linking gp39 with a cytotoxic drug (e.g. see columns 10-11, Utility of the Invention).

Further, Armitage (U.S. Patent No. 6,264,951) (prior art of record) discloses that oligomeric CD40L as agonists, while monomeric CD40L acts as antagonists (e.g. see column 10, paragraphs 2-3). Here, monomeric CD40L antagonists are useful for treating autoimmune diseases encompassed by the claimed methods.

It is noted that Lazarus et al. (Transfusion 39: 818-823, 1999) discloses that the soluble 18 KDa CD40L of the claimed invention cannot inhibit secondary IgG production from memory B cells (see Results, particularly pages 820-821 and Figure 3). Although Lazarus et al. discloses that soluble 18 KDa CD40L could prevent an increase in cell proliferation under certain conditions in a mixed-lymphocyte culture, this 18 KDa CD40L could not inhibit a MLR (see page 821 and Figure 4). Therefore, it appears that the soluble 18 KDa CD40L of the claimed invention may be able to inhibit certain immune responses associated with T cell function and alloimmune responses, soluble 18 KDa CD40L appears limited in the conditions of inhibiting alloimmune responses or T cell immune responses. Also, the Discussion acknowledges that the mechanisms of action by the ability of soluble 18KDa CD40L to inhibit a secondary alloimmune in a SCID mouse engrafted with human lymphocytes is unclear.

Nannizzi-Alaimo et al. (Circulation 105: 2849-2854, 2002) reports that soluble CD40L is a prothrombotic and proinflammatory protein which can contribute to thrombotic and inflammatory complications (See entire document, including Abstract).

In addition, the claims encompass preventing the diseases selected from the group set forth in claim 30. There is insufficient objective evidence that the claimed soluble 18 KDa CD40L can prevent such diseases, including diabetes, arthritis and SLE as set forth in claim 30. For example, the claimed targeted diseases and conditions set forth in claim 30 are treated after the diagnosis of such conditions and diseases.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies of inhibiting alloimmune or T cell responses with a known CD40L agonist, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent a sufficient number of working examples providing evidence which is reasonably predictive that the claimed methods are effective for treating or preventing alloimmune or T cell mediated immune responses with the agonistic soluble 18 KDa CD40L employed in the claimed invention.

4. Claim 27 is objected to in that "Cell" should be "cell".

Claim 30 is objected to in that "sleroderma" should be "scleroderma", "sjorgen's" should be "Sjorgen's", "myesthenia" should be "myasthenia"; and "thrombocyotpenic" should be "thrombocytopenia".

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claim 27 is rejected under 35 U.S.C. § 102(e) as being anticipated by Armitage et al. (U.S. Patent No. 6,264,951 (see entire document, including Detailed Description of the Invention).

Armitage et al. teach methods of administering oligomeric (see entire document, including column 10, paragraphs 2-3 and column 21, paragraph 1). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations of inhibiting anti-HLA alloimmune and T cell responses would be inherent properties of the referenced methods of administering soluble oligomeric CD40L. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.

7. Claim 27 is rejected under 35 U.S.C. § 102(e) as being anticipated by Aruffo et al. (U.S. Patent No. 6,376,459 (see entire document, including Detailed Description of the Invention; also see columns 15-17).

Aruffo et al. teach methods of administering soluble oligomeric CD40L (see entire document, including Detailed Description of the Invention; also see columns 15-17). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations of inhibiting T cell responses would be inherent properties of the referenced methods to administer oligomeric soluble (CD40CR) (i.e. CD40L). It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.

8. Applicant's amended claims have obviated the previous rejections under 35 U.S.C. § 102(e) and 35 U.S.C. § 103(a) as being unpatentable over Armitage et al. (U.S. Patent No. 6,264,951 AND/OR Aruffo et al. (U.S. Patent No. 6,376,459) in view of Black et al. (U.S. Patent No. 6,440,418) wherein ITP was known to be associated with difficulties associated with alloimmune responses, as evidenced by Harrington et al. (Vox San 51: Suppl. 2: 18-21, 1986) as the claims read on the use of oligomeric CD40L as an antagonist.

Although the prior art Armitage et al. (U.S. Patent No. 6,264,951 AND/OR Aruffo et al. (U.S. Patent No. 6,376,459) references teach the use of oligomeric CD40L as agonists, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Therefore, the rejections under 35 U.S.C. § 102(e) and 35 U.S.C. § 103(a) as being unpatentable over Armitage et al. (U.S. Patent No. 6,264,951 AND/OR Aruffo et al. (U.S. Patent No. 6,376,459) have been maintained, given the breadth of instant claims 24 and 27 to read on inhibiting any T cell response.

9. No claim is allowed.

Applicant is invited to consider amending the claims to recite limitations that read on platelet alloimmunization.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
August 11, 2003

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
RGH Group 1600
8/11/03